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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,538	07/19/2001	Josephine Egan	14014.0346U1	5705

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EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/762,538	Applicant(s) EGAN ET AL.	
	Examiner Dong Jiang	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *39-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-52* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED OFFICE ACTION

Applicant's election with traverse of Group II invention, claims 12-22, 27-31 and 33, in Paper No. 9, filed on 28 October 2002 is acknowledged. The traversal is on the ground(s) that the Examiner has not shown that a serious burden would be required to examine all the claims, which is required by MPEP for restriction requirement. This is not found persuasive for the reasons set forth in the last Office Action, paper No. 8, mailed on 26 September 2002. For instance, Group II invention is distinct from Groups V-VIII inventions, wherein Group II invention is directed to a population of insulin-producing cells, and a method of differentiating insulin-producing cells with a growth factor of *exendin-4* or homologues and fragments thereof, whereas Groups V-VIII inventions are directed to a method of treatment using insulin-producing cells generated by contacting *a growth factor*, which reads on any or all growth factor. Further, Groups VI and VIII inventions require additional step of altering the surface antigen of the cells. Thus, much more broader and non-coextensive searches are required for Groups V-VIII inventions, which would constitute an undue search burden on the examiner.

The applicants further traverse that Groups II and IV are related as Group IV is directed to an in vivo use of a method of differentiating insulin-producing cell using exendin-4, and Group II is directed to the method of differentiation, thus, the method and its in vivo use can readily be examined together without serious burden. This argument is persuasive. Upon further reviewing the present claims, the Examiner decides to rejoin Groups I-IV inventions, and the restriction requirement of Groups I-IV is withdrawn.

The requirement between (I-IV) and groups V-VIII is still deemed proper and is therefore made FINAL.

Currently, claims 1-52 are pending, and claims 1-38 are under consideration. Claims 39-52 are withdrawn from further consideration as being drawn to a non-elected invention.

Formal Matters:

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the

instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c).A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions,Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Applicant is advised that should claim 11 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Objections and Rejections under 35 U.S.C. §101 and §112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3-12, and 14-22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1, 3-12, and 14-22, as written, do not sufficiently distinguish over cells as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claim products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified". See MPEP 2105.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially homologous" in claims 1, 12, 23, 27, 32, 33, 34, and 36 is a relative term, which renders the claims indefinite. The term "substantially homologous" is not defined by the claim, and the specification indicates that substantially homologous means a polypeptide sequence of at least 5 contiguous amino acids of either GLP-1, exendin-4. or growth factors having amino acid sequences *substantially homologous* thereto (page 16, lines 16-20), which still does not provide a clear standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to what degree of the sequence homology it is "substantially" homologous.

Claims 4 and 15 are indefinite for the recitation of "non-islet cells". By definition, "islet cells" are a cluster of cells, which does not specify a type of cells, and is not limited to islets of Langerhans'. Therefore, it is unclear what is intended by "non-islet cells", and the metes and bounds of the claims cannot be determined.

Claim 37 is indefinite for the recitation of "by bolus at least once". The term "bolus" is generally used in the art to denote a single, large dose. Therefore, it is not clear what the metes and bounds of "bolus" are, if it can be a repetitive dose. Further, as there is no cure for diabetes at the present time, one-time treatment does not seem to be likely to be effective. As such, the metes and bounds of the claims cannot be determined.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 32 and 33 are directed to a method of promoting pancreatic amylase producing cells to produce both insulin *and amylase* using GLP-1 or exendin-4. However, the experiment results provided in the specification indicate otherwise. The specification discloses that GLP-1 and insulin, either alone or combined with CCK, did not influence amylase release, and exendin-4 did not appear to influence amylase release by cultured rat pancreatic acinar cells, AR42J (Exmple 4, page 48, lines 17-20, and Fig. 15). Further, in view of the prior art, Raufman et al. (J. Biol. Chem., 1992, 267(30): 21432-37) reports that neither GLP-1 nor exendin-4 was able to stimulate amylase release from dispersed acini from guinea pig pancreas (page 21434, the left column, the paragraph below Table II, and Table II). Thus, a skilled artisan would not know how to use the present invention for the purpose of promoting pancreatic amylase producing cells to produce both insulin and amylase using GLP-1 or exendin-4 as claimed because both the experiment results in the instant application and the prior art indicate that neither GLP-1 nor exendin-4 can stimulate amylase release.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-10, 12, 14-21, 23, 26, 27, 30, 31 and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Eng, US 5,424,286.

Eng teaches that GLP-1 and exendin-4 are useful insulinotropic agent, and can be used in treatment of diabetes mellitus (column 1, lines 49-58, the abstract, column 4, and Examples 2, 4 and 5), and that exendin-4 is suited for the treatment of patients with diabetes, both type I and type II (column 2, lines 51-53). In Eng's study (Column 6, lines 34-37), bolus doses of GLP-1 or exendin-4 was given to the animal model mimicking diabetes (hyperglycemic state), and a glucose-dependent isulinotropic response to GLP-1 or exendin-4 was shown, with exendin-4 having more potent effect (Example 2 and Figure 2). Although Eng does not state explicitly the effect of GLP-1 or exendin-4 on converting non-insulin-producing cells into insulin-producing cells, such a converted population of cells inherently exists in the treated animals as the prior art consists of same steps described in the present claims. Since the present invention is merely a newly discovered mechanism/result of a known process, and newly discovered results of known processes directed to same purpose are inherent, the instant claims are not patentable over the prior art. Further, it is indicated in MPEP that when a claim recites using an old composition or structure (e.g. anti-VLA-4 antibodies, anti- 4 antibodies, anti- 1 antibodies) and the use is directed to a result or property of that composition or structure, then the claim is anticipated. See MPEP 2112.02. Therefore, the cited reference anticipates the present claims.

Claims 2, 13, 29, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Raufman et al. (J. Biol. Chem., 1992, 267(30):21432-27).

Raufman discloses that a GLP-1 analogue, GLP-1(7-36) interacts with exendin receptors on dispersed acini from guinea pig pancreas (the abstract). In Raufman's study, dispersed acini from guinea pig pancreas were treated *in vitro* with either GLP-1 or exendin-4,

and the effect of the compounds on amylase release from the treated acini was analysed (Table II). Although the reference is silent about the effect of GLP-1 or exendin-4 on converting non-insulin-producing cells of acini into insulin-producing cells, such a converted population of cells inherently exists in the treated acini as the prior art consists of same steps described in the present claims. Therefore, for the same reasons addressed above, the cited reference anticipates the present claims.

Claims 1, 3-10, 23, 26, and 31 are also rejected under 35 U.S.C. 102(b) as being anticipated by Dupre (WO 95/31214, provided by applicants).

Dupre discloses a method of treating type I diabetes with a GLP-1 analog (GLIP) by ways such as i.v. infusion, and indicates that the use of GLIP in treating type I diabetes provides improved glycemic control, thus to reduce diabetic complications (page 4, lines 26-30, page 7, the third paragraph, and Example 1). As such, a population of insulin-producing cells converted from non-insulin-producing cells would inherently exists in the treated patients as the prior art consists of same steps described in the present claims. Therefore, for the same reasons addressed above, the cited reference anticipates the present claims.

Claim 31 is also rejected under 35 U.S.C. 102(b) as being anticipated by Mashima et al. (Endocrinology, 1996, 137(9): 3969-76, provided by applicants).

Mashima discloses a method of enriching a population of cells for insulin-producing cells by treating cells with a growth factor such as hepatocyte growth factor (HGF), and demonstrates that pancreatic AR42J cells derived from acinar cells, when treated with HGF, were converted into insulin-producing cells (the abstract). The cite reference, therefore, anticipates the present claim 31.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 22, 24 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eng, US 5,424,286, as applied to claims 1, 3-10, 12, 14-21, 23, 26, 27, 30, 31, and 36-38 above.

The teachings of Eng's are reviewed above. The reference does not specifically teach contacting cells with said compound for at least 24 hours as claimed. However, given the current state of the art, determination of an appropriate way of treatment with a drug is well within the purview of a person of ordinary skill in the art, and therefore, the 24 hour period is considered prima facie obvious in the absence of any unexpected result.

Claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dupre (WO 95/31214, provided by applicants), as applied to claims 1, 3-10, 23, 26, and 31 above.

The teachings of Dupre's are reviewed above.

The reference does not specifically teach continuous infusion with said compound for at least *24 hours* as claimed. However, given the current state of the art, determination of an appropriate regimen of treatment with a drug is well within the purview of a person of ordinary skill in the art, and therefore, the 24 hour period is considered prima facie obvious in the absence of any unexpected result.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
1/8/03

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER